Initial Management of Acute Pancreatitis

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KEYWORDS

• Acute pancreatitis • Early phase • Fluid resuscitation • Pain • Nutrition • Antibiotics • Endoscopic retrograde cholangiopancreatography

KEY POINTS

- The initial management of acute pancreatitis (AP) is continually evolving, with new evidence challenging previous practices and influencing clinical approaches.
- Goal-directed moderate fluid resuscitation (FR) is now preferred over aggressive FR due to the harmful outcomes associated with the latter.
- Effective pain management and early oral nutrition are crucial components.
- Antibiotics and antifungal therapy should be administered only when suspected of infected pancreatic necrosis or other concomitant infections rather than for prophylactic purposes.
- The etiology of AP should be addressed to avoid relapse.

INTRODUCTION

Acute pancreatitis (AP) is a frequent condition and a leading cause of admission for gastrointestinal disease with significant associated costs and increasing incidence.[1,2]

AP is a heterogeneous illness. Two-thirds of the cases will have a mild course of the disease with rapid recovery; however, one-third of the patients will develop local complications and/or organ failure, which are associated with worse outcomes.[3] The global mortality rate in AP is around 2% to 4%, but in patients with severe disease (presence of organ failure lasting >48 h), this rate increases up to 50%.[3]

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Although we have no specific therapy for the early phase of AP, evaluation of prognosis, moderate fluid resuscitation (FR), adequate pain management, as well as judicious nutritional support, antibiotic use, and endoscopic retrograde cholangiopancreatography (ERCP) are the cornerstones of initial management of this disease.

In this review, the authors will focus on an evidence-based approach to the initial management of AP and the evaluation of etiology to prevent recurrence.

EARLY PROGNOSIS

After the initial diagnosis of AP, it is important to monitor the patient and assess the likelihood of developing moderately severe or severe disease to optimize initial treatment and the subsequent strategy to follow. Briefly, patients with obesity,[4] advanced age,[4] high blood urea nitrogen,[5] or hematocrit[6] have increased risk of poorer outcomes. Many prognostic models have been created combining different parameters to predict severity (Ranson score,[7] Acute Physiology and Chronic Health Examination II,[8] Systemic Inflammatory Response Syndrome [SIRS],[9] Bedside Index for Severity in Acute Pancreatitis [BISAP]…[10]). SIRS and BISAP (**Fig. 1**) are 2 easily applicable and validated tools that could help initially and are simpler than others. SIRS has a high negative predictive value when not present in the first 24 hours[9–11] and a BISAP $\geq$3 is linked with increased mortality.[10]

Despite the availability of many severity prediction systems, none have shown clear superiority over others, and generally, they have low positive predictive value.[12]

FLUID RESUSCITATION

Since the late 1990s, FR has been considered one of the most important pillars in the management of AP, due to a series of findings that indirectly suggested that aggressive FR improved the evolution of the disease. For example, in observational studies, it

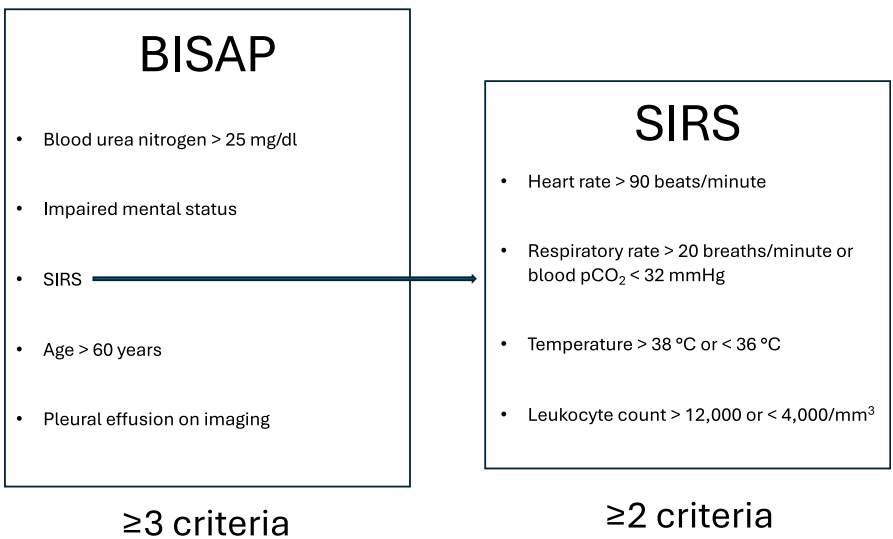

Fig. 1. Bedside index for severity in acute pancreatitis and systemic inflammatory response syndrome criteria. BISAP, Bedside Index for Severity in Acute Pancreatitis; 3 or more criteria are associated with increased mortality. SIRS, systemic inflammatory response syndrome; 2 or more criteria are associated with worse outcomes.

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was described that patients with pancreatic necrosis had a higher hematocrit.[6] It was hypothesized that hemoconcentration compromised blood flow to the pancreas, favoring the development of pancreatic necrosis, which could be theoretically prevented by aggressive FR in the earliest phase of the disease. It seemed to support this theory that patients who die of AP have higher blood urea nitrogen levels than those who survive,[5] suggesting that hypovolemia was associated with mortality. Also, those patients with poorer FR in the first 24 hours compared to the first 3 days had worse outcomes.[13] On the other hand, observational studies did not describe a direct relationship between the volume of fluids administered and a better disease course.[14,15]

Several single-center randomized clinical trials (RCTs) showed heterogeneous results. Two trials from the same group enrolling severe pancreatitis showed that more aggressive regimens increased mortality among other adverse outcomes.[16,17] A clinical trial in patients without baseline SIRS suggested that a more aggressive regimen was associated with a faster recovery.[18]

In 2022, the international multicenter RCT WATERFALL was published.[19] In this study, patients with AP were randomized to receive aggressive FR (a 20 mL/kg bolus followed by a 3 mL/kg/h infusion) versus moderate FR (1.5 mL/kg/h infusion preceded by a 10 mL/kg bolus only in patients with hypovolemia). In the first interim analysis (249 patients), there was a non-statistically significant trend toward worse efficacy outcomes in the aggressive arm, with a clearly higher incidence of fluid overload (21 vs 6%, $P<.01$). This lack of safety of the aggressive arm led to the discontinuation of the study. Following this trial, the previously described moderate protocol is the treatment of choice in patients with pancreatitis (**Fig. 2**).[20]

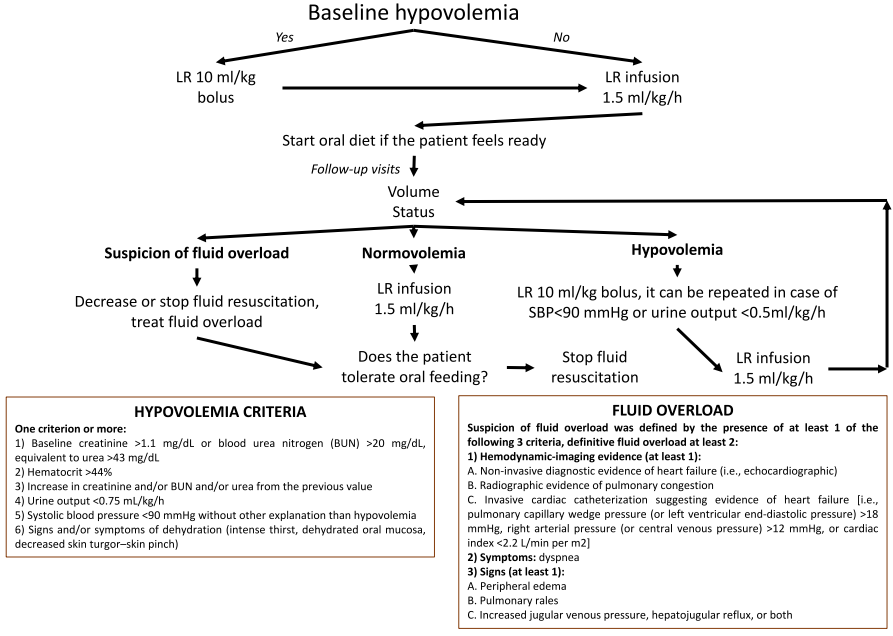

Fig. 2. Fluid resuscitation according to the WATERFALL findings. LR, lactated Ringer solution; SBP, systolic blood pressure. (*Adapted from* de-Madaria E, Buxbaum JL, Maisonneuve P, et al. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. Sep 15 2022;387(11):989-1000. https://doi.org/10.1056/NEJMoa2202884)

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Different types of fluids have been studied both in acute conditions (sepsis, during the postoperative period) and specifically in patients with AP. Colloids generally do not seem better than crystalloids[21] and may even have more adverse effects.[22] Several clinical trials have compared lactated Ringer's solution versus normal saline. Lactated Ringer's solution contains lactate, which has anti-inflammatory properties,[23] and normal saline has been associated with hyperchloremic acidosis.[24] Meta-analyses of studies in pancreatitis[25,26] have shown advantages in the use of lactated Ringer's solution, such as lower severity, less admission to the intensive care unit (ICU), or fewer local complications, but the results were heterogeneous, so new RCTs are needed to assess this topic.

MANAGEMENT OF SYMPTOMS

Abdominal pain is the main symptom associated with AP. It is usually intense and greatly impacts the patient's disease experience. Analgesia, therefore, is one of the fundamental aspects of its treatment. However, evidence on pain management is scarce, and few good quality RCTs have been performed in this setting, so no clear analgesic strategy has been defined or can be recommended.

In a recent review and meta-analysis of RCTs,[27] epidural anesthesia was demonstrated to be the most effective treatment in reducing pain in the first 24 hours. Still, it was similar to opioids after 48 h, so it could be ideal for early treatment of patients with uncontrolled pain and then transition to other treatment lines. It has been suggested that epidural anesthesia is associated with reduced 30-day mortality in AP admitted to the ICU, but a recent RCT failed to demonstrate improved outcomes.[28] Epidural analgesia is limited to a critical care scenario, so its use cannot be generalized to all AP.

Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used in AP. Opioids are sometimes preferred due to their rapid and potent analgesic effect. However, different meta-analyses have demonstrated that they have a similar effect to NSAIDs in the first 24 h or the need for rescue analgesia.[27,29] A recent double-blinded RCT (not included in previous meta-analyses) comparing buprenorphine versus diclofenac[30] demonstrated higher efficacy of buprenorphine, requiring less rescue medication, having longer pain-free intervals, and similar adverse events.

Concerns about opioids regarding their secondary effects (respiratory depression, constipation, risk of dependence) and possible influence on AP severity have been raised.[31] In a recently published prospective cohort study,[32] the use of opioids after admission day, or for more than 6 days, was associated with increased severity. However, this was an observational study, so causality cannot be inferred from these results.

NSAIDs are probably less used than opioids due to their known gastrointestinal and kidney-related adverse events, even if their occurrence in AP is rare.[29] In 2 RCTs, diclofenac[33] and dexketoprofen[34] proved to be similar to opioids (tramadol). Still, in the other 2 RCTs, diclofenac had lower efficacy than pentazocine[35] or buprenorphine.[30] Type of NSAID or opioid used, and their dosage should be taken into account as their properties differ from one to the other and could influence their analgesic power. Moreover, evidence regarding NSAID efficacy or adverse events beyond 24 hours is lacking.

Metamizole is also a suitable option for AP pain with a better gastrointestinal and cardiovascular profile that is frequently used as a first-line treatment in some countries.[36] Its prescription is restricted in some regions due to its agranulocytosis risk.[37] Metamizole may be similar to or better than morphine in the first 48 hours to relieve pain.[38] However, this was an underpowered pilot study, and more studies are needed to confirm these results.

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Another interesting drug in AP pain management is cyclooxygenase-2 (COX-2) inhibitors. In a recent RCT,[39] administering intravenous parecoxib for 3 days, followed by oral celecoxib twice daily for 7 days, was compared to conventional treatment. Pain scores dropped more rapidly in COX-2 inhibitors arm and required less rescue medication. Moreover, in this arm, significantly fewer patients developed severe AP. Further studies are needed to confirm these results.

Intravenously administered local analgesics, such as lidocaine, have no role in an AP scenario as they have the lowest overall efficacy on pain relief compared to the other modalities explained earlier.[27]

A systematic review and meta-analysis demonstrated better outcomes in pain relief when acupuncture was combined with conventional treatment than conventional treatment alone.[40] However, more rigorous studies are needed.

Patient-controlled analgesia (PCA) is frequently used in postoperative pain. However, evidence on its use and outcomes in patients with AP are still scarce. A recently published retrospective study in AP about the use of PCA showed no benefit of this approach, with longer hospital stay, days to enteral nutrition, and likelihood of being discharged under opioids. In this study, men, patients with alcohol-induced AP, and African Americans were less likely to be administered PCA.[41] RCTs are needed to evaluate the role of PCA in patients with AP; these trials should focus on relevant clinical outcomes and pain relief, preferably utilizing Patient-Reported Outcome Measures (PROMs). A 7-symptom free-to-use scale, the PAN-PROMISE scale (**Table 1**), has been developed in AP to allow a global view of patients' subjective experiences.[42] This scale is also a tool for assessing the impact of new treatments and administration routes on acute pancreatitis symptoms.[19]

NUTRITION

In the past, it was believed that one crucial aspect of AP recovery was maintaining "pancreatic rest" to prevent stimulation and secretion of pancreatic enzymes, which was thought to worsen the course of the disease. Evidence in the last 2 decades contradicts this longstanding belief.[43] Several RCTs have shown that early oral refeeding is safe and associated with a shorter length of hospitalization and costs in mild AP without increasing oral intolerance or complications.[44–47]

Table 1
PAN-PROMISE symptom scale, a patient-reported outcome measurement

Symptom	Score
Pain, especially in the abdomen, chest, or back	
Abdominal distention (bloating, sensation of excess gas)	
Difficulty eating, sensation of food being stuck in the stomach	
Difficulty with bowel movements (constipation or straining on bowel movements)	
Nausea and/or vomiting	
Thirst	
Weakness, lack of energy, fatigue, difficulty moving	

This Questionnaire Should be Answered Directly by the Patient
Please Indicate for Each Symptom the Highest Intensity You Have had in the Last 24 h
The Intensity is Scored Between 0 (None) and 10 (Maximum Possible Intensity of the Symptom)
The PAN-PROMISE scale can be used freely without permission from the authors. (de-Madaria E et al, Gut 2021 https://doi.org/10.1136/gutjnl-2020-320729)

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When reintroducing food after fasting, there's no need to start with a clear liquid diet and gradually progress to solid foods. Beginning with soft or solid foods directly is well tolerated and associated with a shorter length of hospitalization.[46,48–50]

Previously, early enteral nutrition by nasojejunal tube was recommended in predicted severe AP. On the one hand, nasojejunal tube feeding was thought to prevent stimulation of the pancreas and improve the course of the disease, as previously discussed. On the other hand, meta-analyses of studies comparing enteral versus parenteral nutritional support showed that enteral nutrition was associated with better outcomes, including lower mortality.[51] Finally, studies suggested that enteral nutrition was beneficial for the gut, preventing bacterial translocation.[52]

In a landmark study by the Dutch Pancreatitis Study Group, patients with predicted severe AP were randomized to nasojejunal tube feeding started within 24 h versus oral diet started 72 hours after presentation, with tube feeding provided if the oral diet was not tolerated (on-demand enteral nutrition).[53] Both treatment arms had similar results. With this approach, 69% of patients in the on-demand enteral nutrition arm tolerated oral feeding in the first 72 h, avoiding nasojejunal tube feeding. Therefore, an oral diet is recommended in predicted severe or even severe AP, restricting enteral nutrition for patients who cannot tolerate it after at least 3 to 4 days.[47,53]

In different meta-analyses comparing nasogastric versus nasojejunal tube feeding,[54,55] there was no difference in mortality, risk of aspiration, pneumonia, pain exacerbation, gastrointestinal symptoms, energy balance, or hospital stay. Nasojejunal tube is recommended in some guidelines when patients need to undergo necrosectomy and do not tolerate oral feeding[56]; however, we should take into account that this recommendation is based on the lack of studies assessing the use of a nasogastric tube in this setting.

A standard polymeric formula for enteral nutrition is recommended[56] as there is no evidence of better outcomes for elemental or semi-elemental formulas.[57,58]

Parenteral nutrition might be needed in patients not tolerating oral diet in whom enteral nutrition is contraindicated.[59] Another possible indication is when nutritional requirements are not met with enteral nutrition alone.[56] In these cases, the supplementation with L-glutamine at 20 g/Kg/day is recommended based on different meta-analyses (although with risk of bias due to small sample sizes, confounding factors, and heterogeneity) that showed a reduction in complications and mortality.[60] There is a need for larger clinical trials assessing this specific topic in AP to confirm these results.

Other immuno-nutrients are not generally recommended.[56] There is some evidence regarding the benefits of omega-3 fatty acids, mostly when administered in parenteral nutrition[61] but larger and more rigorous RCTs are needed.

We cannot recommend the use of probiotics. The PROPATRIA trial raised concerns about their safety, as the probiotic group had higher mortality rates than the placebo group (16% vs 6%), and it did not decrease the infection rate.[62]

Another important aspect to assess following an episode of AP is the possibility of the patient developing exocrine pancreatic insufficiency (PEI) and, therefore, the need for pancreatic enzyme replacement therapy (PERT). After an AP episode, PEI can occur in up to 60% of the cases; this percentage decreases to 35% in the follow-up.[63] Consequently, the presence of PEI and the use of PERT should be considered in patients with AP. PEI can be screened with fecal elastase determination, but which patients may benefit from this remains to be determined. Fecal elastase has been associated with a high false-positive rate in chronic pancreatitis.[64] PEI has been demonstrated to be more common after an episode of necrotizing or severe AP and

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alcohol etiology.[63] Ongoing studies will clarify the role of fecal elastase, PEI after AP, and the impact of PERT and how this might affect patient's quality of life.[65]

ANTIBIOTICS AND ANTIFUNGAL THERAPY

There is a wide range of antibiotic use in AP (31%–81%).[66] There are situations in which the use of antibiotics is strongly indicated, such as in positive cultures or high suspicion of acute cholangitis, in case of acute cholecystitis, in the presence of nosocomial infections, such as central catheter infection, urine tract infection, or pneumonia, and pancreatic necrosis infection (whether it is highly suspected or confirmed by Gram or culture of drained material). In addition, there are situations where it is not worthwhile to administer antibiotics, such as in a patient with sterile necrotizing pancreatitis or with predicted severity without suspicion of infection where prophylactic antibiotics are prescribed to prevent pancreatic infections. Several meta-analyses demonstrate that antibiotic prophylaxis is not associated with a lower frequency of necrosis infection or improvement in other outcomes.[67]

The problem is deciding whether to use antibiotics in patients with AP who show signs or lab parameters of inflammation, such as leukocytosis, or are febrile without other clear signs of infection. According to a retrospective study of nearly 10,000 patients, the variables most associated with antibiotic administration in AP were leukocyte count, C-reactive protein, amylase, and lipase levels in the blood, none of which are specifically associated with infection.[66] A single-center RCT compared a procalcitonin-based antibiotic administration strategy (a molecule that is elevated in the event of bacterial infection) versus clinician judgment.[68] The procalcitonin-based strategy lowered antibiotic use significantly, with no change in diagnosed infectious diseases or side effects. The evidence for using procalcitonin to give antibiotics is clearer in mild pancreatitis than in moderate to severe AP.[69] Thus, in case of doubt, procalcitonin could be a helpful tool in deciding whether to start or stop antibiotics.

Antibiotics that penetrate well into pancreatic collections, necrosis, and pancreatic tissue are carbapenems, ciprofloxacin + metronidazole, and high-dose cephalosporins.[70]

In patients with necrotizing AP, can contribute to a fungal infection such as ICU admission, the use of central venous catheters, parenteral nutrition, and the use of broad-spectrum antibiotics.[71] Invasive candidiasis may reach up to 18% in patients treated for severe AP in the ICU[72] and 27% of patients under treatment for infected walled off necrosis develop fungal infection.[73] However, antifungal drugs are not recommended as prophylactic therapy as there is no RCT assessing its use. Although it is sometimes difficult to distinguish between colonization and infection, antifungal therapy is only advised when fungal infection is confirmed.[74]

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Gallstones are the main etiology behind AP, typically triggered by their lodgment in the common bile duct or ampulla.[75] This is also the mechanism associated with the development of acute cholangitis; this potentially life-threatening condition requires urgent ERCP, preferably in less than 24 hours,[76] as it has been associated with reduced in-hospital mortality, 30-day mortality, organ failure, and length of hospital stay.[77–79]

However, the role of ERCP in patients with AP has been a point of debate during the last decades, and different RCTs have assessed this topic.

In earlier RCTs, the results seemed to be positive for early ERCP,[80–83] but the outcomes measured and populations included were heterogeneous.

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Table 2
Randomized controlled trials evaluating the role of urgent endoscopic retrograde cholangiopancreatography in patients with acute pancreatitis without cholangitis or obstructive jaundice

First Author, Year	Inclusion Criteria	Patients, Urgent ERCP/ Control	Time to ERCP	Mortality Rate (%)	Morbidity Rate (%)	Organ Failure (%)	Local Complications (%)
Fölsch et al,[84] 1997	Biliary AP with bilirubin < 5 mg/dL	126/112	<72 h (from onset of symptoms)	7.9/3.6	46.0/50.9	34.1/25.9	23.0/22.3
Oría et al,[85] 2007	Biliary AP without cholangitis	51/51	<72 h (from onset of symptoms)	6.0/2.0	21/18	25.5/19.6	11.8/9.8
Schepers et al,[86] 2020	Predicted severe biliary AP without cholangitis	117/13	<24 h (from emergency department admission) or <72 h (from onset of symptoms)	6.8/8.8	38.5/44.2	14.5/15.9	18.8/15.0

Abbreviations: AP, acute pancreatitis. ERCP, endoscopic retrograde cholangiopancreatography.

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In the abscence of cholangitis, 3 different RCTs (Table 2) have not demonstrated an improvement in clinical outcomes with urgent ERCP in patients with AP.[84–86] Even in patients with demonstrated stones or sludge located in the common bile duct by endoscopic ultrasound followed by ERCP, urgent ERCP was not associated to reduced major complications or mortality compared to conservative treatment.[87] A consensus is that patients with AP and concomitant acute cholangitis should undergo urgent ERCP.[80–83]

ETIOLOGY ASSESSMENT

One of the most important aspects of managing AP is assessing its etiology (Table 3)[88], as depending on that, the cause can be treated, and new episodes can be prevented.

Biliary etiology is the most common cause of AP, accounting for approximately 60% of cases.[3] Cholecystectomy during the same admission, when AP is mild, is more effective in reducing relapse of AP and other gallstone-related complications and

Table 3
Etiology of acute pancreatitis (TO IMAGINE acronym)

Category	Etiologies
T: Toxic	Alcohol Tobacco Scorpion venom
O: Obstructive	Gallstones/biliary sludge Solid/cystic tumors Ductal postnecrotic stricture Congenital malformations: pancreas divisum, anomalous pancreaticobiliary junction Sphincter of Oddi dysfunction Duodenal obstruction/diverticulum/duplication cyst Choledochocele/choledochal cyst
I: Iatrogenic	Endoscopic Retrograde Cholangiopancreatography Pancreatic biopsy Surgery Drugs Dialysis
M: Metabolic	Hypertriglyceridemia
A: Autoimmune	Autoimmune pancreatitis type 1 and 2 Immune checkpoint inhibitors
G: Genetic	PRSS-1 SPINK-1 CFTR CPA1 CASR CLD2 CTRC
I: Infection	Virus Bacteria Fungi Parasites
N: Nobody knows	Idiopathic acute pancreatitis
E: Endocrine	Primary hyperparathyroidism

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costs compared to interval cholecystectomy without an increase in surgical adverse events.[89,90] In case of moderate to severe AP, cholecystectomy should be postponed after inflammatory signs have diminished, usually around 4 to 6 weeks (before 8 weeks) after the initial episode.[91,92] Other measures include support for smoking and drinking cessation in AP of toxic origin, treatment of hypertriglyceridemia, withdrawal of drugs associated with pancreatitis, etc.

SUMMARY

The initial management of AP is continually evolving, with new evidence challenging previous practices and influencing clinical approaches. Severity prediction tools are currently not accurate. Goal-directed moderate FR is now preferred over aggressive FR due to the harmful outcomes associated with the latter. Effective pain management and early oral nutrition are crucial components. Antibiotics and antifungal therapy should be administered only when suspected of infected pancreatic necrosis or other concomitant infections rather than for prophylactic purposes. Procalcitonin can help decide whether to start antibiotics. Urgent ERCP should be reserved for cases involving acute cholangitis. The etiology of AP should be addressed to avoid relapse. Same-admission cholecystectomy in mild biliary AP can reduce AP recurrence. Some gaps remain in the initial management of AP. New studies are underway and will bring new insights to this topic.

CLINICS CARE POINTS

- A fluid resuscitation rate at 1.5 mL/kg/h infusion (preceded by a 10 mL/kg bolus in patients with hypovolemia) is safer and tends to have better efficacy outcomes than more aggressive fluid resuscitation. Lactated Ringer solution may be associated with improved outcomes, but new studies are needed.
- Early oral feeding with soft or solid food is the optimal nutritional approach for most patients with acute pancreatitis. If nutritional support is needed, enteral nutrition is preferred over parenteral nutrition. In the absence of gastric outlet obstruction, a nasogastric tube is generally favored over a nasojejunal tube.
- A standardized protocol for pain management cannot be currently recommended. Opioids and NSAIDs are options for initial pain management, but more comparative studies are needed. Cyclooxygenase-2 inhibitors show promise in managing pain and reducing the severity of AP. It remains to be clarified which patients might benefit from epidural analgesia and whether it is associated with better outcomes.
- Antibiotic prophylaxis for pancreatic infections is not effective. Antibiotic therapy is indicated in case of gram or culture-positive infection, or a high probability of infection based on clinical, laboratory, and imaging findings. In doubtful situations, serum levels of procalcitonin may be a good marker for bacterial infection and, therefore, the need for antibiotics. Antifungal therapy is only indicated when infection is confirmed.
- Urgent ERCP is not better than delayed ERCP in patients with AP without associated cholangitis, even if there is a proven obstruction of the common bile duct, as it does not improve clinical outcomes. Cholecystectomy is recommended on admission for mild AP and in moderate-severe AP should be performed around 4 to 6 weeks after the initial episode.

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DISCLOSURES

The authors have nothing to disclose related to this manuscript.

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